Systemic Therapy for Clear Cell Sarcoma: A Systematic Review and Individual Patient Data Meta-Analysis

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Background

Clear cell sarcoma (CCS) is an ultra-rare, EWSR1::ATF1 / CREB1 fusion-driven sarcoma of soft tissue, bone, and the gastrointestinal tract (GI CCS / GNET). Broad soft tissue sarcoma trials rarely enroll more than a few patients with CCS, so systemic therapy is chosen by extrapolation from other sarcomas or small N studies. We pooled every published CCS-specific outcome to ask which systemic therapy is most effective.

Methods

Register: PROSPERO CRD420261356968; reported to PRISMA 2020.

Search: PubMed/MEDLINE, Embase, Scopus, Web of Science, EBSCO, and ClinicalTrials.gov, inception to 2026, any language.

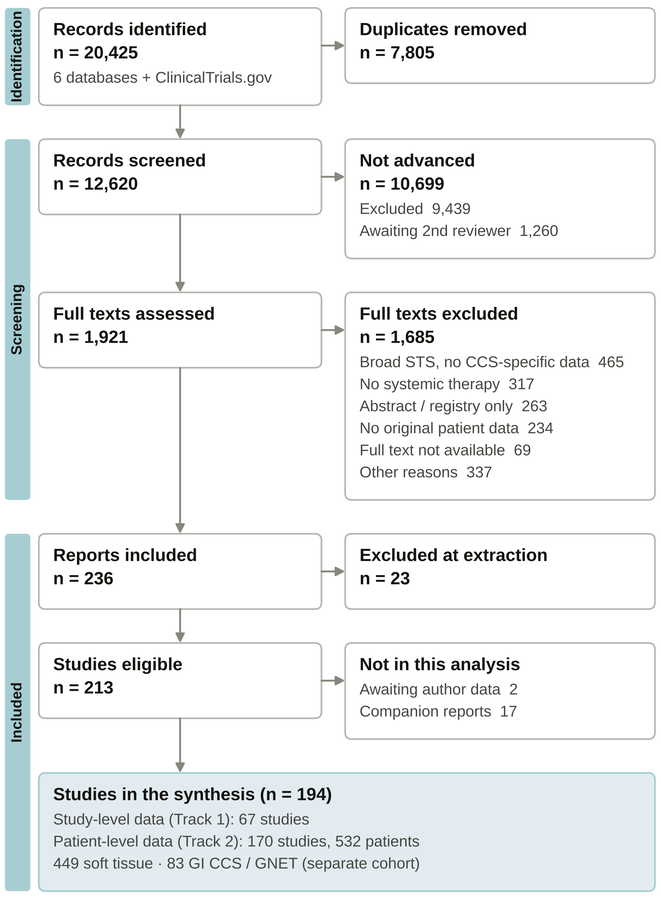
Screen: CCS of soft tissue or bone and GI CCS / GNET, systemic therapy in any setting; CCS of the kidney excluded.

Extract: Study-level data (Track 1) and individual patient data per line of therapy (Track 2), never pooled together; authors asked for unpublished CCS data. **Advanced disease** = any line of therapy for unresectable, recurrent, or metastatic disease (not adjuvant or neoadjuvant).

Confirm and appraise: Tier 1 = EWSR1 fusion, break-apart FISH, or t(12;22) / t(2;22) (primary analysis; all tiers as sensitivity). JBI checklists plus a molecular-confirmation domain: only 41% of 177 appraised studies confirmed CCS molecularly (46% not at all), 56% were at high risk of bias, and 212 of 532 patients (40%) were Tier 1.

Analyze: Exact CIs; random effects (Freeman–Tukey, DerSimonian–Laird) for ≥3 studies; Kaplan–Meier; Cox stratified by study. GI CCS / GNET is always a separate cohort.

Figure 1. PRISMA 2020 Flow of Study Selection



Results

194 studies analyzed

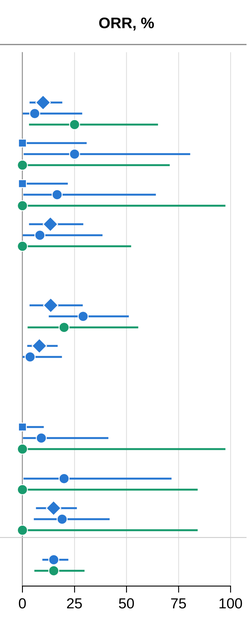
532 patients with individual data

3.0 mo median PFS in soft tissue

15% response rate in both cohorts

Figure 2. Objective Response Rate by Treatment Class, Advanced Disease

Treatment class	◆ Study-level CCS of soft tissue: Studies / patients	ORR (95% CI)	● Patient-level CCS of soft tissue: Responses / lines	ORR (95% CI)	● Patient-level GI CCS / GNET: Responses / lines	ORR (95% CI)
Cytotoxic chemotherapy						
Anthracycline-based	6 / 51	**10% (3–19)**	1 / 17	**6% (0–29)**	2 / 8	**25% (3–65)**
Ifosfamide, no anthracycline	3 / 10	**0% (0–31)**	1 / 4	**25% (1–81)**	0 / 3	**0% (0–71)**
Trabectedin	4 / 15	**0% (0–22)**	1 / 6	**17% (0–64)**	0 / 1	**0% (0–98)**
Other cytotoxic[1]	6 / 22	**13% (3–29)**	1 / 12	**8% (0–38)**	0 / 5	**0% (0–52)**
Targeted therapy						
VEGFR multi-kinase TKI[2]	6 / 36	**14% (3–29)**	7 / 24	**29% (13–51)**	2 / 10	**20% (3–56)**
MET-targeted TKI[3]	4 / 50	**8% (2–17)**	1 / 27	**4% (0–19)**	–	–
Immunotherapy						
Anti-PD-1 / PD-L1	5 / 34	**0% (0–10)**	1 / 11	**9% (0–41)**	0 / 1	**0% (0–98)**
Anti-CTLA-4 ± anti-PD-1	*no study-level data*		1 / 5	**20% (1–72)**	0 / 2	**0% (0–84)**
Checkpoint inhibitor + TKI	7 / 46	**15% (7–26)**	4 / 21	**19% (5–42)**	0 / 2	**0% (0–84)**
All classes[4]	*not pooled across classes*		**21 / 140**	**15% (10–22)**	**6 / 40**	**15% (6–30)**



Study-level pooled ORR in CCS of soft tissue was at most 15% in any class. Patient-level ORR per line was 15% in both cohorts (soft tissue 21/140; GI CCS / GNET 6/40) and highest with VEGFR multi-kinase TKIs (7/24). GI responders: anthracyclines 2/8, VEGFR TKIs 2/10, dabrafenib + trametinib 1, crizotinib + pazopanib 1. Tier 1 (EWSR1-confirmed): 14% in soft tissue (10/69), 15% in GI (5/33). Lines were mostly distant metastatic (soft tissue 63%, with 29% stage not reported; GI 93%); ORR in metastatic lines alone was 16% in both cohorts.

[1] Gemcitabine-, dacarbazine-, or platinum-based, etoposide, vincristine, nitrosoureas. [2] Apatinib, pazopanib, anlotinib, sunitinib, sorafenib. [3] Crizotinib, tivantinib, AMG 337 (crizotinib only at patient level). [4] Includes other or unnamed regimens. Diamond: pooled; square: crude; circle: patient-level, per line. Exact 95% CIs.

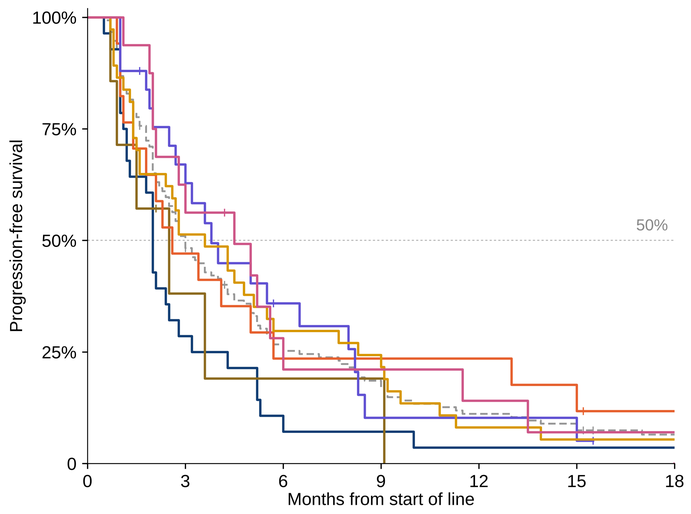
Figure 3. Progression-Free Survival by Treatment Class, Advanced CCS of Soft Tissue

Median PFS by class

2.0–4.5 months

All classes: 3.0 months (95% CI 2.5–3.8), 152 lines
25% progression-free at 6 months

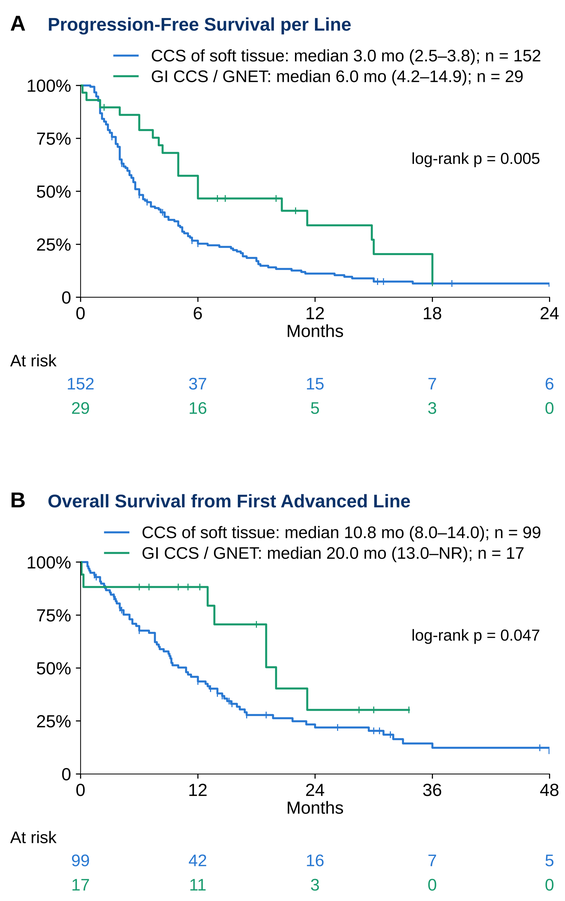
No class was clearly better (log-rank p = 0.20)



Treatment class	Median PFS, mo (95% CI)	6-month PFS	Number at risk						
Anthracycline-based	**2.0** (1.2–2.5)	7%	28	8	3	2	1	1	1
Trabectedin	**2.5** (0.7–9.1)	19%	7	2	1	1	0	0	0
Other cytotoxic[1]	**2.6** (1.1–5.7)	24%	17	8	4	4	4	3	1
VEGFR multi-kinase TKI[2]	**3.8** (2.5–8.0)	36%	25	16	7	2	2	2	0
MET-targeted TKI[3]	**3.6** (1.6–5.5)	30%	37	19	11	9	3	2	2
Checkpoint inhibitor + TKI	**4.5** (2.0–6.0)	21%	16	10	4	3	2	1	1
All classes[4]	**3.0** (2.5–3.8)	**25%**	**152**	**76**	**37**	**25**	**15**	**12**	**7**

Kaplan–Meier PFS per line of therapy (one patient's course of one regimen). Classes with ≥5 lines are plotted; smaller ones (anti-PD-1 / PD-L1, 4 lines; anti-CTLA-4 ± anti-PD-1, 3; ifosfamide, 2) count only in All classes. Class medians ranged from 2.0 to 4.5 months; anthracyclines, the sarcoma default, were shortest (2.0 months). Tier 1 (60 lines): median 4.3 months (2.6–5.2), no class clearly better (p = 0.95). Superscripts as in Figure 2.

Figure 4. Soft Tissue vs GI CCS / GNET, Advanced Disease



(A) PFS per line: median 3.0 vs 6.0 months (log-rank p = 0.005). (B) OS from the first advanced line: 10.8 months (n = 99) vs 20.0 months (n = 17); p = 0.047. Distant metastatic disease made up 64% of soft-tissue and 93% of GI lines; metastatic lines alone gave similar medians (2.8 vs 6.0 months).

Limitations

- Mostly case reports and small series: 56% of appraised studies were at high risk of bias and 46% gave no molecular confirmation of CCS.
- Patient-level analyses are per line of therapy, so one patient can contribute several lines.
- Adjuvant and neoadjuvant therapy could not be compared fairly: it was given to patients with higher-risk disease.
- Dual review and data from 2 author groups are still pending.

Conclusions

- Responses are rare in advanced CCS: ORR 15% in both cohorts.
- Progression is fast: median PFS 3.0 months in soft-tissue CCS and no class above 4.5 months. Anthracyclines gave 2.0 months and 10% ORR.
- VEGFR multi-kinase TKIs gave the most responses (29%) and the most patients progression-free at 6 months (36%).
- GI CCS / GNET has longer PFS (6.0 vs 3.0 months) and OS (20.0 vs 10.8 months) and should stay a separate cohort.

Acknowledgments. We thank the investigators who shared individual patient data: Andrea Ferrari (Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy); Binghao Li (Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China); Gianmaria Miolo (Centro di Riferimento Oncologico di Aviano IRCCS, Aviano, Italy); and Jyoti Sharma and Sameer Bakhshi (All India Institute of Medical Sciences, New Delhi, India).